Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment*

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Summary

The possibility that exposure to environmental tobacco smoke (ETS) may increase the lung cancer risk of nonsmokers has become a cause of public concern. It is unknown whether the levels of carcinogens in the diluted sidestream smoke of tobacco products that reach the nonsmoker's lung are sufficient to induce cancer. Available epidemiologic studies suggest a slight increase in the relative risk of lung cancer in nonsmokers due to exposure to ETS created by a smoking spouse. However, not all studies have found a significant association. The epidemiologic studies are examined in the light of the criteria of judgment of causality, including strength of association, consistency, temporality, methodological issues, and biological plausibility. Suggestions for further research, including studies in high-exposure populations and greater attention to histology, are proposed.

Introduction

Epidemiologists, chemists, biologists, physiologists, physicians, and public health officials have given much attention to the association of environmental tobacco smoke (ETS) exposure and the development of lung cancer in nonsmokers. A biological basis for such an association clearly exists because smoke constituents demonstrated to be carcinogenic in laboratory animals are inhaled and retained by the nonsmoker. Metabolites of tobacco-specific smoke constituents have been identified in the saliva, blood, and urine of nonsmokers after exposure to ETS (Greenberg et al. 1984; Hoffmann et al. 1984; National Academy of Sciences 1986; USDHHS 1987; Sepkovic et al. 1988). Several epidemiological studies have found a positive association between ETS exposure – usually defined as being due to a smoking spouse – and lung cancer (Hirayama 1981; Trichopoulos et al. 1981; Correa et al. 1983; Sandler et al. 1985; Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Pershagen et al. 1987). Other studies have found no significant association (Garfinkel 1981; Chan and Fung 1982; Koo et al. 1983; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986). No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

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The epidemiological study of weak associations is burdened with problems that may yield artifactual positive findings or may show negative findings where a real association exists. The association of ETS and lung cancer risk, even if weak, would still be of concern as a public health problem in that most people are at one time or another exposed to smoke from burning tobacco products and the exhaled pollutants of tobacco smokers. A weak association in epidemiology requires careful examination and an understanding of the variables in question and all of the factors influencing the association (Wynder 1987).

In this overview we critically examine the published studies on ETS exposure and lung cancer to determine whether the evidence presented to date permits a sound conclusion as to causation.

General Exposure to ETS

At the outset we need to emphasize that an association between ETS and lung cancer must be deemed possible. A recent survey of self-reported exposure in a hospitalized population revealed that 66% of men and 60% of women had ETS exposure in childhood; 32% of the men and 61% of the women reported ETS exposure in the home in adulthood; and 60% of the men and 62% of the women who worked outside the home reported ETS exposure at work (Kabat and Wynder, unpublished data, 1987).

Critical Assessment

The first Surgeon-General's Report on Smoking and Health, published in 1964 (USPHS 1964), clearly delineated the criteria of judgment for causality. These criteria included: the magnitude of the association, consistency, temporality, and biological plausibility. Since these criteria were considered necessary to prove causation for a strong association, namely, active smoking and lung cancer, they should be equally required to determine the causality of weak associations (Wynder 1987). Let us examine the epidemiological evidence linking ETS with lung cancer in respect to these criteria.

Strength of the Association

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer (Table 1). If the observed relative risk is small, it is important to determine whether the effect could be due to biased selection of subjects, confounding, biased reporting, or anomalies of particular subgroups.

Consistency

If an association is real, internal consistency should be apparent within and between different studies. The majority, but not all of the studies of ETS and lung cancer have shown a positive association for ETS-exposure due to a smoking spouse (Table 1). In most of the studies, the confidence interval includes 1.0. While the prospective study by Hirayama (1981a) among Japanese women showed a significant association with the husband's smoking (largely adenocarcinomas), the prospective study among American

Table 1. Summary of results of studies relating lung cancer risk in married women to their husbands' smoking habits

	Relative risk	95% Confidence interval
Prospective studies		
Hirayama (1981)	1.63	1.25–2.11
Garfinkel (1981)	1.18	0.90–1.54
Case-control studies		
Trichopoulos et al. (1981)	2.1	1.18–3.78
Chan & Fung (1982)	0.75	0.44–1.30
Correa et al. (1983)	2.03	0.83–5.03
Koo et al. (1983)	1.54	0.90–2.64
Kabat & Wynder (1984)	0.79	0.26–2.43
Wu et al. (1985)	1.2	0.6 –2.5
Garfinkel et al. (1985)	1.12	0.74–1.69
Lee et al. (1985)	1.03	0.41–2.47
Akiba et al. (1986)	1.48	0.88–2.50
Pershagen et al. (1987)	1.28	0.75–2.16

Table 2. Distribution of lung cancer by histologic groups in smokers and never-smokers. (From Kabat and Wynder 1984)

	Smokers		Never-smokers	
	Males (N = 1882) [%]	Females (N = 652) [%]	Males (N = 37) [%]	Females (N = 97) [%]
Kreyberg I	63	52	35	21
Kreyberg II	32	43	54	74
Mixed and undifferentiated/anaplastic	5	5	11	5

women by Garfinkel (1981) did not. It has been suggested that Japanese and American women are exposed to different levels of ETS due to different conditions in the two countries. Such differences could account for this disparity (Hirayama 1981b).

Within those studies presenting specific histologic analysis, differences exist in respect to the type of lung cancer involved. In active smokers, tobacco smoke exposure has a causative effect predominantly on squamous and small cell types of lung cancer (Kreyberg I), with a lesser, though still significant causative effect on the glandular type (Kreyberg II) (Wynder and Stellman 1977). Among nonsmokers, however, the glandular type of lung cancer predominates among both men and women (Kabat and Wynder 1984) (Table 2). The effect of ETS would thus be expected to be primarily responsible for the higher rate of adenocarcinomas among nonsmokers. The studies by Dalager et al. (1986) and Pershagen et al. (1987), however, suggest that the effect of ETS exposure is limited to induction of squamous cell lung cancer (Table 3). If this were, in fact, the case, then only the squamous or small cell type of lung cancer in nonsmokers

Table 3. Histology-specific odds ratios for spouse smoking from two studies

Study	Histologic type	N	Odds ratio	95% C.I.
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33– 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91– 9.10
	Other	18	1.31*	0.48– 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 –11.4
	Other	47	0.8	0.4 – 1.5

would be affected by ETS. Clearly, it is important that investigations of the effect of ETS exposure on lung cancer development in nonsmokers take histology into account, so as to determine whether an effect of ETS is limited to certain histological types.

Since smoking is more prevalent in lower income groups, at least among men, lung cancer in nonsmoking women in these groups should have a higher incidence. Thus, the influence of the level of education on smoking habits in the examined population needs to be considered as a possible confounder. Few studies to date have done this.

Methodological Issues

A particular concern in weak associations is reporting bias, that is, potentially differential reporting of exposures between cases and controls. In terms of ETS, does the lung cancer patient report exposure to tobacco smoke, be it at work, at home, at social functions, in childhood or adulthood, differently than the control? The case is likely to have a different attitude toward this question than does the control, a handicap not applicable to prospective studies. It needs to be determined whether the case's attitude towards questions on ETS exposure leads to under- or overreporting. Cases are likely to underreport their own smoking (Lee 1987), and they may tend to overreport their exposure to ETS and other potential hazards that could account for their illness. In studies that use proxy reports, different relatives may respond differently. Garfinkel et al. (1985) provides some insight into this phenomenon by showing that if the response came from the patient, the odds ratio was 1.0, if from the husband it was 0.92, and if from the daughter or son, 3.19 (Table 4). More work is needed on the validity of ETS-exposure information obtained from different relatives before we can evaluate which of these relative risks is closer to the truth.

In general, possible reporting bias represents a serious problem in case-control studies because it can produce a systematic artefact. It is particularly worrisome in that it cannot be effectively measured.

We also need to consider misclassification that can occur in both retrospective and prospective studies. Lee has proposed (Lee et al. 1986; Lee 1987) that the reported ETS effect on lung cancer risk can be explained by a misclassification of smokers as nonsmokers. According to these studies, a substantial percentage of respondents misrepresent their smoking habits. Using a 10.0% misclassification rate of ex-smokers as self-reported neversmokers coupled with the concordance of spouses' smoking habits,

Table 4. Data from Garfinkel et al. (1985) by type of respondent

	Husband's smoking habits at home		
	N of cases	OR	95% C.I.
Self	16	1.00	0.55– 1.74
Husband	34	0.92	0.63– 1.34
Daughter/son	48	3.19	0.91–11.19
Other	36	0.77	0.57– 1.03

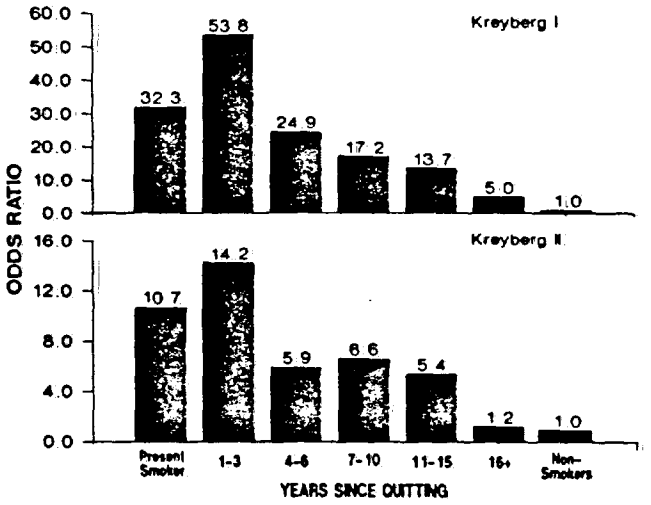

Fig. 1. Odds ratio of male ex-smokers for Kreyberg I (N = 687) and Kreyberg II (N = 301) lung cancer by years since quitting (controls = 6534). Source: American Health Foundation data

Lee calculated that an apparent increase in lung cancer risk can be obtained among nonsmokers married to smokers that approximates the increased risk observed in a number of epidemiologic studies (Lee 1987). At the extreme, Garfinkel et al. (1985) showed that 40% of lung cancer cases classified as "nonsmokers" in the hospital chart were in fact smokers as determined by interview. Although such a high rate of misclassification does not occur when cases are interviewed personally, to some extent denial is likely to occur even then, particularly among ex-smokers who had stopped smoking ten or more years ago. The risk of lung cancer among long-term ex-smokers, and even among ex-smokers who quit more than 16 years earlier, does remain elevated above the rate among those who never smoked (Fig. 1). Denial of past smoking may also not be uncommon in populations where smoking is or was socially unacceptable, as is the case among older Japanese women.

Table 5. Percent of lung cancer cases who never smoked by histologic group (A.H.F. data)

	Males				Females			
	KI*		KII**		KI*		KII**	
	[%]	N	[%]	N	[%]	N	[%]	N
1969–1973	1.2	488	5.6	142	10.7	103	23.7	76
1974–1976	1.6	887	3.0	305	16.4	263	25.3	146
1977–1980	2.1	628	4.6	390	5.6	231	22.0	245
1981–1985	1.4	725	5.6	463	6.8	311	16.6	284

* Kreyberg I
** Kreyberg II

Another problem for epidemiologists involves subgroup analysis (Stallones 1987). Investigators are likely to examine numerous subgroups, and then prefer to present those subgroups that best fit the hypothesis. This tendency represents an inherent problem in epidemiology. The investigator should at a minimum give an idea of how many subgroups were originally examined and how many subgroups were discarded.

Temporality

One of the factors that led to the conclusion that active smoking causes lung cancer was that the increase in cigarette consumption preceded the increase in lung cancer rates, first in men and later in women. Enstrom (1979) has reported an increase in the lung cancer rate in nonsmokers over recent years, suggesting that factors in addition to personal cigarette smoking influence lung cancer mortality rates. The groups examined, however, are not strictly comparable, and misclassification of smokers as nonsmokers in the national surveys needs to be considered. Our data from a long-term, hospital-based case-control study do not indicate an increase in the percentage of male nonsmokers with lung cancer in either of the two main histologic groupings (Kreyberg I and II) over the last 30 years (Table 5).

In fact, the percentage of nonsmokers with lung cancer among women has declined, which may be a consequence of the diminishing pool of women who have never smoked.

Biological Plausibility

Several studies have demonstrated that most tumorigenic agents are present in undiluted sidestream smoke in higher concentrations than in mainstream smoke (Hoffmann et al. 1983; National Academy of Sciences 1986; Hoffmann and Wynder 1986) (Table 6). Biochemical studies indicate that nonsmokers exposed to ETS have levels of nicotine or cotinine in the blood or urine that are about 1/100th the level seen in active smokers (Table 7) (Jarvis et al. 1984; National Academy of Sciences 1986). Some of the nicotine measured in the blood and urine represents nicotine that is absorbed by the saliva of nonsmokers and does not reach the lung directly (Jarczyk et al. 1987). It is important to

Table 6. Distribution of compounds in undiluted cigarette mainstream smoke (MS) and sidestream smoke (SS)

Nonfilter cigarettes

	MS	SS/MS
(A) Vapor phase		
Carbon monoxide	10 – 23 mg	2.5– 4.7
Carbon dioxide	20 – 40 mg	8 – 11
Benzene	20 – 50 µg	10
Formaldehyde	5 – 100 µg	0.1–≈50
Acrolein	50 – 100 µg	8 – 15
Acetone	100 – 250 µg	2 – 5
Hydrogen cyanide	400 – 500 µg	0.1– 0.25
Hydrazine	24 – 43 ng	3.0
Ammonia	50 – 170 µg	40 – 170
Methylamine	11.5 – 28.7 µg	4.2– 6.4
Nitrogen oxides	50 – 600 µg	4 – 10
N-nitrosodimethylamine	10 – 180 ng	20 – 100
N-nitrosopyrrolidine	2 – 110 ng	6 – 30
(B) Particulate phase		
Particulate matter	15 – 40 mg	1.3– 1.9
Nicotine	1 – 2.5 mg	2.6– 3.3
Phenol	60 – 140 µg	1.6– 3.0
Catechol	100 – 350 µg	0.6– 0.9
Hydroquinone	110 – 300 µg	0.7– 0.9
Aniline	360 ng	30
2-Toluidine	30 – 160 ng	19
2-Naphthylamine	4.3 – 27 ng	30
4-Aminobiphenyl	2.4 – 4.6 ng	31
Benz(a)anthracene	40 – 70 ng	2 – 4
Benzo(a)pyrene	10 – 40 ng	2.5– 3.5
N'-Nitrosonornicotine	120 –3,700 ng	0.5– 3
NNK	120 – 950 ng	1 – 4
Cadmium	100 ng	7.2
Nickel	20 –3,000 ng	13 – 30
Polonium-210	0.03– 1.0 pCi	?

note that nicotine occurs in ETS primarily as a vapor phase constituent rather than in the particulate matter of the aerosol as is the case in mainstream cigarette smoke (Eudy et al. 1987). Measurement of nicotine or its metabolites will, therefore, not reflect the proportional uptake of particulate matter from ETS. In the light of our present knowledge of dose-response in carcinogenesis and because the carcinogenic activity of tobacco smoke as measured in animal systems is relatively low, the question needs to be raised whether the carcinogenic potential of inhaled ETS suffices to induce lung cancer. Hoffmann and Hecht (1985) have proposed nicotine-derived nitrosamines in ETS as organ-specific carcinogens for the lung. It is possible that these chemicals reach the lungs in sufficient dose to induce neoplastic changes. These carcinogens may also be formed endogenously from inhaled or ingested nicotine and appropriate nitrosating agents (Hoffmann and Hecht 1985). Tumor promoters are less likely to play a role in ETS

Table 7. Approximate relations of nicotine as a parameter between non-smokers, passive smokers and active smokers[a]. (From Jarvis et al. 1984)

Nicotine/cotinine	Non-smokers without ETS exposure No. = 46		Non-smokers with ETS exposure No. = 54		Active smokers No. = 94
	Mean value	% of active smokers value	Mean value	% of active smokers value	Mean value
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml)					275
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[a] Differences between non-smokers exposed to ETS compared with non-smokers without exposure
* $p < 0.01$
** $p < 0.001$

carcinogenesis than in active smoking because of their much lower concentration. In general, tumor promoters are effective only when applied repeatedly in relatively large amounts.

In considering the existing data on ETS exposure and lung cancer, it is noteworthy that Auerbach et al. (1961) showed only minor histological changes in the bronchial epithelium of nonsmokers and found that the ciliated columnar epithelium that covers their bronchi were largely intact. Deposition of carcinogenic smoke particulates can take place only upon inhibition of the protective functioning of the lung clearance system. Squamous cell lung cancer can arise only from ciliated columnar cells that have undergone squamous metaplasia.

An active smoker with each puff from a cigarette inhales a volume of 35–50 ml of a concentrated aerosol containing 3–5 billion particles per ml that adversely affect the protective cilia and mucous defense system of the bronchi (Ferin et al. 1965). The passive smoker is at no time exposed with such force to such a highly polluted inhalant. Furthermore, ETS particles are more likely to be deposited in the upper respiratory tract and not predominantly in the bronchi as is the case in active smoking. Thus, our respiratory defense system may be able to deal more readily with the relatively lighter deposition of particles and exposure to volatiles in ETS, as the observation by Auerbach et al. (1961) would suggest.

Future Studies

Future epidemiological studies on the association of ETS with lung cancer should attempt to avoid the pitfalls discussed above. The definitive evidence that a factor causes

human cancer requires support from descriptive, metabolic, and molecular epidemiology.

Beyond extension of prospective studies, such as those now in progress by Garfinkel and Stellman at the American Cancer Society, we suggest:

1) Continuing ongoing case-control studies with special reference to histologic type and careful consideration of methodological issues.
2) Estimating the relative importance of ETS exposure in different settings – in the home, in the workplace, in social situations, and during transportation.
3) Further studying lung cancer rates among pipe and cigar smokers, and, if feasible, among nonsmokers exposed to ETS from these products.
4) Studying lung cancer incidence in groups occupationally exposed to high levels of ETS at their worksite such as waiters, bartenders, train conductors, airplane personnel, and office workers.
5) Studying bronchial epithelium in autopsy material of established never-smokers whose exposure to ETS is known.
6) Determining the incidence of lung cancer by histological type in confirmed never-smokers.
7) Comparing the presence of adducts of tobacco-specific carcinogens with DNA in smokers, passive smokers, and "never-smokers" (Hoffmann and Hecht 1985; Hecht et al. 1987).

In summary, verification of the possible association of ETS and lung cancer represents an important challenge to epidemiologists, laboratory scientists, and public health authorities. The public is entitled to inhale the cleanest possible air regardless of whether ETS is proven to be cancer-inducing. Additional efforts on the part of epidemiologists are required to firmly establish the nature and significance of the reported associations between passive smoking and lung cancer.

References

Akiba S, Kato S, Blot WJ (1986) Passive smoking and lung cancer among Japanese women. Cancer Res 46:4804–4807

Auerbach O, Stout AP, Hammond EC, et al (1961) Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Engl J Med 265:253–267

Chan WC, Fung SC (1982) Lung cancer in non-smokers in Hong Kong. In: Grundman E (ed) Cancer campaign, vol 6. Cancer epidemiology. Fischer, Stuttgart, pp 199–202

Correa P, Fontham E, Pickle L, Lin Y, Haenszel W (1983) Passive smoking and lung cancer. Lancet 2:595–597

Dalager NA, Pickle LW, Mason TJ, et al (1986) The relation of passive smoking to lung cancer. Cancer Res 46:4808–4811

Enstrom JE (1979) Rising lung cancer mortality among nonsmokers. J Natl Cancer Inst 62:755–760

Eudy LW, Thome FA, Heavner DL, Green CR, Ingebrethsen BJ (1985) Studies on the vapor-phase distribution of environmental nicotine by selected trapping and detection methods. Pres. 39th Tobacco Chemists Res Conf, 1985, p 25

Ferin J, Urbankova G, Vlokova A (1965) Influence of tobacco smoke on the elimination of particles from the lungs. Nature 206:515–516

Garfinkel L (1981) Time trends in lung cancer mortality among non-smokers and a note on passive smoking. J Natl Cancer Inst 66:1061–1066

Garfinkel L, Auerbach O, Joubert L (1985) Involuntary smoking and lung cancer: A case-control study. J Natl Cancer Inst 75:463–469

Greenberg RA, Haley NJ, Etzel RA, Loda FA (1984) Measuring the exposure of infants to tobacco smoke: nicotine and cotinine in urine and saliva. N Engl J Med 310:1075–1078

Hecht SS, Carmella SG, Trushim N, Foiles PG, Lin D, Rubin YM, Chung FL (1987) Investigations on the molecular dosimetry of tobacco-specific N-nitrosamines. International Agency for Research on Cancer, Lyon [IARC Sci Publ 84:423–429]

Hirayama T (1981a) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study in Japan. Br Med J 282:183–185

Hirayama T (1981b) Nonsmoking wives of smokers have a higher risk of lung cancer [Letter]. Br Med J 283:916–917

Hoffmann D, Hecht S (1985) Nicotine-derived N-nitrosamines and tobacco-related cancer: Current status and future directions. Cancer Res 45:935–944

Hoffmann D, Wynder EL (1986) Chemical constituents and bioactivity of tobacco smoke. In: Zaridze DG, Peto R (eds) Tobacco: A major international health hazard. International Agency for Research on Cancer, Lyon, IARC Sci Publ 74:145–65

Hoffmann D, Haley NJ, Brunnemann KD, Adams JD, Wynder EL (1983) Cigarette sidestream smoke: formation, analysis and model studies on the uptake by nonsmokers. US-Japan meeting "New Etiology of Lung Cancer", Honolulu, Hawaii, March 21–23, 1983

Hoffmann D, Haley NJ, Adams JD, Brunnemann KD (1984) Tobacco sidestream smoke: uptake by nonsmokers. Prev Med 13:608–613

Jarczyk L, Slerer G, Maltzan C, Luu HT, Adlkofer F (1987) Intake of nicotine from ETS via different inhalation routes. Proceedings of Third International Conference on Indoor Air Quality (in press)

Jarvis M, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y (1984) Biochemical markers of smoke absorption and self-reported exposure to passive smoking. J Epidemiol Comm Health 38:335–339

Kabat GC, Wynder EL (1984) Lung cancer in nonsmokers. Cancer 53:1214–1221

Koo LC, Ho JH-C, Saw D (1983) Active and passive smoking among female lung cancer patients and controls in Hong Kong. J Exp Clin Cancer Res 4:365–375

Lee PN (1987) Lung cancer and passive smoking: association an artefact due to misclassification of smoking habits? Toxicol Letts 35:157–162

Lee PN, Chamberlain J, Alderson MR (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br J Cancer 54:97–105

National Academy of Sciences, National Research Council (1986) Environmental tobacco smoke. Measuring exposures and assessing health effects. National Academy Press, Washington DC

Pershagen G, Hrubec Z, Svenssen C (1987) Passive smoking and lung cancer. Am J Epidemiol 125:17–24

Sandler DP, Everson RB, Wilcox AJ (1985) Passive smoking in adulthood and cancer risk. Am J Epidemiol 121:37–48

Sepkovic DW, Axelrad CM, Colosimo SG, Haley NJ (1988) Measuring tobacco smoke exposure: clinical applications and passive smoking. 80th Annual Meeting and Exhibition of the Air Pollution Control Association, New York, NY, June 21–26, 1987 (in press)

Stallones RA (1987) The use and abuse of subgroup analysis in epidemiological research. Prev Med 16:183–194

Trichopoulos D, Kalandidi A, Sparros L, MacMahon B (1981) Lung cancer and passive smoking. Int J Cancer 27:1

[USDHHS] US Dept Health and Human Services, Public Health Service, Office of Smoking and Health (1984) The health consequences of smoking: cardiovascular disease. A Report of the Surgeon General. USDHHS, US Govt. Printing Office, [DHHS Publ No (PHS) 84-50204] Washington DC

[USDHHS] US Dept Health and Human Services, Public Health Service, Centers for Disease Control (1987) The Health Consequences of Involuntary Smoking, a Report of the Surgeon General. USDHHS, US Govt. Printing Office, [DHHS (CDC) Publ No 87-8398], Washington DC

[USPHS] US Public Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service (1964) US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control [PHS Publ No 1103] US Govt Printing Office, Washington DC

Wu AH, Henderson BE, Pike MC, Yu MC (1985) Smoking and other risk factors for lung cancer in women. J Natl Cancer Inst 74:747–751

Wynder EL (ed) (1987) Workshop on guidelines to the epidemiology of weak associations. Prev Med 16:139–212

Wynder EL, Stellman ST (1977) Comparative epidemiology of tobacco-related cancers. Cancer Res 37:4608–4622